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NOVEL COMBINATION PRODUCT COMPRISING AN ANTIFUNGAL AGENT AND
CROTAMITON AS AN ANTIFUNGAL ACTIVITY ENHANCER AND DERMATOLOGICAL OR
COSMETIC COMPOUNDS COMPRISING SAME
[NOUVEAU PRODUIT DE COMBINAISON COMPRENANT UN AGENT ANTIFONGIQUE ET
DU CROTAMITON COMME POTENTIALISATEUR DE L'ACTIVITE DE L'AGENT
ANTIFONGIQUE, ET COMPOSITIONS DERMATOLOGIQUES ET/OU COSMETIQUES LE
COMPRENANT]

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Novel Combination Product Comprising an Antifungal Agent and Crotamiton as an Antifungal Activity Enhancer and Dermatological or Cosmetic Compounds Comprising Same /i*

(57) Abstract

Novel combination product comprising as association of, firstly, an anti-fungal agent selected from the 1-hydroxy-2-pyridones such as ciclopirox or octopirox and the physiological acceptable salts thereof and, secondly, crotamiton as an anti-fungal agent activity enhancer. The present invention also concerns a dermatological or cosmetic compound comprising this combination product and at least one pharmaceutically acceptable excipient.

The present invention pertains to new compounds that are useful in dermatology and/or cosmetology that offer improved anti-fungal activity. /1

The treatment of skin fungal infections is quite limited because of the lack of therapies. The problems associated with these pathologies, secondary effects, lack of response to treatment or development of resistance of the germs, are a reality of the field.

Among skin diseases causes by fungi we can distinguish those due to yeast and those due to dermatophytes.

Skin infections caused by the yeasts *Pityrosporum* or *Candida* have seen renewed outbreaks especially because of the increase of skin allergies and because of the number of patients presenting acquired immune syndrome.

Indeed, the lipophilic yeasts *Pityrosporum orbicular* and *Pityrosporum ovale* are present as saprophytes of the skin, but when

* Number in the margin indicates pagination in the foreign text.

they are transformed into their active hypha form known under the name of *Malassezia furfur*, it leads to variegated pityriasis. This very common eruption in young adults is present in the form of small circular areas with white, red or maroon peeling skin. The lesions are produced in the area of the trunk, on the proximal part of the arms or legs and can converge. Establishment of the germ is confirmed when depigmentation of the skin is present. This is due to the production of a dicarboxylic acid by the yeast, which results from inhibition of tyrosinase. This effect, contrary to the synthesis of melanine, has an unpleasant appearance and comprises one of the first clinical indications in the patient, skin colonization by this germ being painless.

During treatments it is essential that all of the infected areas be included in order to be certain that the problem has been eradicated. Patients subjected to oral corticotherapy or who have had their immune system compromised, can develop a massive infestation. When a clinical detection is not made and when topical steroids are prescribed, an accelerated eruption can develop.

Benefits for seborrheic dermatitis have been renewed since the appearance on the market of Ketoconazole, for the purpose of oral or topical treatment, the inflammatory components of this affection /2 also caused by *Pityrosporum*. This has led to recognition of a disease that initially was not observed but is now recognized as *pityrosporum folliculitis*. Its main manifestation is folliculitis of

the trunk of young and middle age patients and it is frequently associated with seborrheic dermatitis.

The latter manifests in the form of eruptions with grayish peeling of the scalp, ears, inguinal folds of the trunk and back.

Skin peeling in the area of the folds of the eyelids and nostrils are also a manifestation of attack by the yeast.

It is likely that very many external factors play a role in altering the saprophytic effects of *Pityrosporum* in variegated pityriasis and seborrheic dermatitis, which induces modification of skin behavior of the yeast.

The other pathologies involved in yeast are superficial skin and mucous candidiasis. *Candida albicans* is the pathogenic agent most frequently encountered but other types can also be present.

Since the species of *Candida* multiply easily in a warm and humid atmosphere, cases of surface candidiasis accumulate in the area of the axillary's folds or adjacent to the body orifices. Some erythematous and moist plates are visible and can give rise to pustules on the edges of the lesions. Of course, some promoting factors, such as treatment with broad spectrum antibiotics, systemic steroids and other immunosuppressive molecules will favor the emergence of bucco-digestive cases of candidiasis.

Certain types of diabetes and hypoparathyroidism can have as a consequence chronic paronychia and require additional topical treatment.

Finally, in the case of immune deficiency, there might also be a granulomatous reaction as in the case of digestive candidiasis. When the diseases are severely immune system compromising, there is dissemination of the yeast that is both systemic and skin related.

But separately from the aforementioned irritating effects, an immunological response has been described with these yeasts. It is humeral and cellular. High rates of anti-pityrosporum serum antibodies during dandruff cases have been shown.

Moreover, seborrheic dermatitis is more common in patients that have atypical background, cervico-cephalic atypical dermatitis, with the presence of orbicular anti-pityrosporum specific Ig E in which /3 the rate is highly correlated with the severity of the disease. With respect to dermatophytoses we can mention athlete's foot, scalp disease as well as all cases of onychomycosis.

Given all of these pathologies, few therapies are actually effective.

The imidazoles require a minimum of three weeks of twice daily regiment, skin lesions frequently being extended, and the patient frequently lacks enough product to be able to treat all of the body lesions (visible especially in light of Wood by presence of a clear yellow color). The application of shampooing with ketaconazole has been mentioned to improve the application but the patient might fail his treatment when a large surface area of the back is involved. In

addition, the imidazoles are fungi-static and the probability of resistance is therefore high.

Other local treatments such as shampoos based on zinc pyrithion, selenium sulfite or coaltar show that remission is not complete after about one month of treatment.

Therefore there is a real need for an anti-fungal product that would have different qualities such as efficacy, quickness of action and offer excellent skin tolerance.

Therefore, the present invention deals with a new combination product, in which the synergistic combination offers improved anti-fungal activity, active against strains that are generally resistant to the traditional anti-fungal agents, especially to imidazoles such as econazole.

The present invention also pertains to a dermatological and/or cosmetic compound that includes the said synergic association of products.

The synergy can be demonstrated by calculation of the Fic index (Fractional inhibitory Concentration Index) or FFC of a product A that is defined as follows.

$$FFCA = \text{CMF of the product in combination} / \text{CMF of the product alone}$$

CMF that defines the minimal fungicidal concentration for which one obtained a diminution of 4.Log 10 of the cultured inoculums in 5 minutes of contact at 20°C.

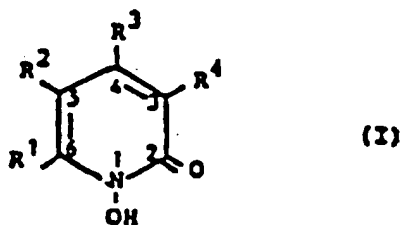
The combination of two anti-fungal agents A and B is synergistic if the sum of the FFC (or FFC index) (FFCA + FFCB) is less than or equal to 0.75.

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As the FFC index value is lower, the synergy is more important.

It has been thought that there is a simple additive function for index values between 0.75 and 1.1 and indifference in the interval between 1.1 and 2. Beyond that the combination is considered antagonistic.

The new product according to the invention consists on the one hand of an anti-fungal agent selected among 1-hydroxy-2-pyridones with the general formula I.



in which R_1 represents a saturated hydrocarbon remainder having from 6 to 9 atoms of carbon,

one of the remainders R_2 and R_4 represents an atom of hydrogen and the other represents an atom of hydrogen or the methyl or ethyl group, and

R_3 represents an alkyl remainder having 1 or 2 atoms of carbon, and their physiologically acceptable salts.

and on the other hand some crotamiton, as an enhancer of anti-fungal activity of the 1-hydroxy-2-pyridone.

The dermatological and/or cosmetic compound according to the invention contains a synergistic combination of 1-hydroxy-2-pyridone with general formula I, as defined earlier, and crotamiton, with at least one pharmaceutically acceptable excipient.

By saturated we mean a hydrocarbon remainder that does not contain any multiple aliphatic bonds such as ethylene or acetylene bonds.

Preferably R1 is an alkyl or cycloalkyl remainder, and in this case a cyclohexyl remainder which can be bonded to the pyridone nucleus by an alkaline, or can even be substituted by an alkyl group.

R1 can also represent an aromatic radical or an aromatic radical bonded to the pyridone nucleus by an alkaline remainder.

The aromatic radical is preferably a phenyl group, possibly /5 substituted by one or several alkyl groups.

Among the compounds with general formula I that are useful according to the present invention we will mention in particular 1-hydroxy-4-methyl-6-n-hexyl-, -6-isohexyl-, -6-n-heptyl- or -6-iso-heptyl-2-pyridone, 1-hydroxy-4-methyl-6-octoyl- or -6-iso-octyl-2-pyridone in particular in the form of 1-hydroxy-4-methyl-6- (2,4,4-trimethylpentyl)-hydroxy-4-methyl-6-cyclohexyl-2-pyridone, 1-hydroxy-4-methyl-6-cyclo-hexylmethyl- or -6-cyclohexylethyl-2-pyridone, the cyclohexyl remainder capable in each case of carrying another methyl radical, 1-hydroxy-4-methyl-6-(2-bicyclo [2.2.1]heptyl)-2-pyridone,

1-hydroxy-3,4-dimethyl-6-benzyl- or -6-dimethylbenzyl-2-pyridone and 1-hydroxy-4-methyl-6(β -phenyl-ethyl)-2-pyridone.

In a preferred manner, the 1-hydroxy-2-pyridone is ciclopirox (R1=cyclohexyl, R2=R4=H and R3=CH3) or octopirox (R1=2,4,4-trimethylpentyl, R2=R4=H and R3=CH3) as well as their physiologically acceptable salts, especially their ethanolamine salt.

The benefit of the 1-hydroxy-2-pyridones resides in their action in the area of protein metabolism of yeasts; that is after having penetrated into the cell and not in the area of ergosterol synthesis, like the imidazoles that operate at the partial level.

The crotamiton, or N-ethyl-N-O-tolylcrotonamide for its part has been described as a scabicide, anti-pruritic or anti-fungal agent.

In a preferred manner the weight ratio of 1-hydroxy-2-pyridone/crotamiton in the combination product according to the invention is between 4/1 and 1/4, preferably in the vicinity of 1.

The ingredients of the new combination product according to the invention are intended to be used simultaneously.

However, they could also be used in combination separately or separated in time.

The same preferred weight ratio between 1-hydroxy-2-pyridone with formula I, as defined earlier and crotamiton, will be studied in the dermatological and/or cosmetic compounds according to the invention.

According to this feature of the present invention the synergistic combination as defined earlier will be presented in the compound with a content between 0.5 and 4% by weight.

The compounds are preferably in the form of shampoos, lotion or even an aerosol solution.

The examples that follow are intended to illustrate the invention without limiting its range in any way. /6

In these examples we will refer to the tables in the appendix that summarize the fungicidal activity of the products alone and combined with raw *Pityrosporum ovale* that is resistant to econazole, and *Candida albicans* ATCC 9021.

EXAMPLE 1: Ciclopiroxolamine/crotamiton Combination

Some strains of *Malassezia furfur* (*Pityrosporum ovale*) were tested for their sensitivity to active principles alone or in combination according to the invention.

The strains came from the Parasitology Laboratory of the Regional Hospital Center of Rangueil of Toulouse (France) and one strain is econazole resistant (eco-R). They were cultivated during trials of solid Dixon medium.

The technique used is original because it uses both the principle of the checkerboard pattern and that of the Afnor standard by filtration on a membrane relative to the fungicide with a germ-molecule contact time of 5 minutes.

It is a macro method which was therefore carried out here with validations for each trial of the control solvent of the molecules (Tween® 20%, ethanol 17% in distilled water).

This solvent slightly inhibits activity of the ciclopiroxolamine, and one should therefore expect better results in practice. The other controls are that of the strength of the strain and efficacy of the products along, or:

- ciclopiroxolamine 4%
- crotamiton 4%

Table 1 presents the geometric averages of the logarithmic reduction on two raw Pityrosporum ovale units in which one is eco-R, the number of trials as well as the efficacy percentage.

The Afnor standard considers that there is a fungicide for a reduction of 4 Log 10 of the inoculums after 15 minutes of contact.

Therefore in this case we have five minutes of 100% activity contact for:

- Crotamiton 4% (product used alone)
- Crotamiton 2%)
-) (synergistic combination)
- Ciclopiroxolamine 2%)

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and 50% activity for

- Ciclopiroxolamine 4% (product used alone)

For technical reasons of solubilization of the molecule, we considered that the greater concentrations of cilopiroxolamine

approached 100% activity at about 6% ciclopiroxolamine. The FFC index is then less than 0.7.

The pH of the totality of these studies was around 8.

EXAMPLE 2: Octopiroxolamine/crotamiton combination

The combination of octopirox with crotamiton was tested according to the methodology of Example 1 on a strain of *Pityrosporum* oval eco-R and *C. albicans* ATCC 9021.

Table 2 presents the results obtained for *P. ovale* eco-R after five minutes of contact for the combination:

- crotamiton 1% - octopirox 1% for which we had 100% efficacy
- while the products alone at double or quadruple concentration are less active.

Indeed, the crotamiton at 4% yields an efficiency of 84% and the octopirox at 2% an efficiency of 45%.

Therefore we see that the ratio of concentration gives us a FFC index less than 0.75.

The same solvent was used and validated for each trial as specified in the Afnor standard.

These results were confirmed on an Afnor reference yeast (*C. albicans* ATCC 9021). The results are summarized in table 3.

The trials of example 2 were carried out with a pH more basic, 9.

TABLE 1

Produits concentra- tions (%) (m/v)	CPO(4)	CPO(2)	CPO(2)	CPO(2)	CPO(2)	Crota (1)	Crota (2)	Crota (4)
Mg	2,05	0,43	1,11	2,90	4,09	0,03	0,77	3,77
n	7	7	3	7	3	7	7	3
2 %activité	50%	10%	25%	75%	100%	1%	20%	100%

Key: 1-Concentration products (%) (m/v); 2-% activity

CPO: ciclopiroxolamine

Crota: crotamiton

Mg: geometric average of Log 10 of the reduction of the number of germs

n: number of independent trials

One sees that a synergy for CPO 2%/Crota 2%: the products alone, with double concentration of CPO 4% or Crota 4%, are less active than their less concentrated combined products.

TABLE 2

Produits (%)	Octo (2)	Octo (1) Crota (1)	Crota (2)	Crota (4)
Mg	1,85	4,07	1,59	3,26
n	2	2	2	2
%activité	45%	100%	40%	83%

Key: 1-products (%); 2-% activity

Octo: Octopyrox

TABLE 3

Produits (%)	Octo (2)	Octo (1)	Octo (1) Crota (1)	Octo (0,5) Crota (1)	Octo (0,5) Crota (1)	Crota (2)	Crota (4)
Mg	3,18	0,36	4,94	0,57	2,54	2,43	4,95
n	3	3	3	2	3	3	3
%activité	60%	7%	100%	10%	50%	50%	100%

Key: 1-products (%); 2-% activity

EXAMPLE 4: Shampoo

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Octopiroxolamine)
or) 0.5 to 2%
Ciclopiroxolamine)
Crotamiton	0.5 to 2%
Decylglucoside (55% solution)	10 g
Disodium cocoamphodiacetate (38% solution)	15 g
Cocamidopropyl betaine (30% solution)	
Cocamide MEA	5 g
Propyleneglycol	2.5 g
Perfume, coloring	
Chelating agent	
Distilled water	QSP
pH adjusted between 7 to 9	100 ml

EXAMPLE 5 Shampoo

Octopiroxolamine)
or) 0.5 to 2%
Ciclopiroxolamine)
Crotamiton	0.5 to 2%
Laurylpolyglucose (50% solution)	10 g
Disodium cocoamphodiacetate (4038% solution)	8 g
Polysorbate 20	1 to 3 g
Hydrogenated talloweth 60	
Myristyl glycol	2 to 3 g
N-hydroxytehl-acetamide (70% solution)	0.5 to 1.5%
Chelating Perfume	
Opacifying agent	
Distilled water	QSP
pH adjusted between 7 to 9	100 ml

EXAMPLE 6: Shampoo

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Octopiroxolamine)
or) 0.5 to 2%
Ciclopiroxolamine)
Crotamiton	0.5 to 2%
Decylglucoside (55% solution)	6 g
Disodium cocoamphodiacetate (38% solution)	15 g
Cocamidopropyl dimethylamino Hydroxypropyl	
Collagen hydrolysis (30% solution)	7 g
Cocamide DEA	3 to 5 g
Glycerin	2 g

Perfume, coloring		
Distilled water	QSP	100 ml
pH adjusted between 7 to 9		

EXAMPLE 7: Shampoo

Ciclopiroxolamine or Octopiroxolamine)	
) 0.5 to 2%	
Crotamiton)	
Ether alkyl sulfate of trienthanolamide (30% solution)		20 to 50%
Dihydroxyethanolamide of Copra fatty acids		
Disodium ethylene diamine		0.15%
Sodium chloride (qs viscosity)		1%
Perfume		
Purified water	QSP	100 ml

It is important to be certain that the pH of these shampoos is adjusted to about 7-9 for reasons of efficacy and better solubilization of the active ingredients. It is quite evident that these formulas are not limiting and that it is important to make certain of the compatibility of surface-active agents with the combination 1-hydroxy-2-pyridone /crotamiton according to the invention.

EXAMPLE 8: Capillary lotion

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Octopiroxolamine)	
or) 0.5 to 2%	
Ciclopiroxolamine)	
Crotamiton		0.5 to 2%
Laurylpyridium chloride		0.01 to 0.100
Dimethicone copolyol		0.10 to 0.50%
Perfume	QS	
Water-alcohol mixture 30% to 30% volume	QSP	100 ml

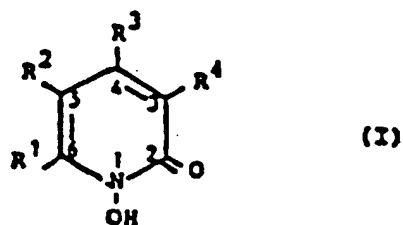
EXAMPLE 9: Aerosol solution

Octopiroxolamine)
or) 0.5 to 2%
Ciclopiroxolamine)
Crotamiton	0.5 to 2%
Cyclomethicone	1 to 5%
Methylol	30 ml
70% N-hydroxyethylacetamide	1 to 5%
Ethyl alcohol	50 ml
Distilled water	QSP
Nitrogen QSP	100 ml
9 bard for pressurization in aerosol container	

CLAIMS

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1. Combination product characterized in that it consists in the combination on one hand of an anti-fungal agent selected among 1-hydroxy-2-pyridones with the general formula 1:



in which R₁ represents a saturated hydrocarbonated remainder having from 6 to 9 atoms of carbon,

one of the remainders R₂ and R₄ represents an atom of hydrogen and the other represents an atom of hydrogen or the methyl or ethyl group, and R₃ represents an alkyl remainder having 1 or 2 atoms of carbon,

and their physiologically acceptable salts,

and on the other hand some crotamiton, as the enhancer of anti-fungal agent activity.

2. Product according to Claim 1 characterized in that in the general formula I, R_1 is an alkyl or cycloalkyl remainder, the said cycloalkyl capable of being bonded to the pyridone nucleus by an alkaline, or even substituted by an alkyl group.

3. Product according to claim characterized in that in the general formula 1, R_1 is an aromatic radical, possibly substituted by one or several alkyl groups which can be bonded to the pyridone nucleus by an alkaline remainder.

4. Product according to Claim 1 characterized in that the anti-fungal agent with the general formula I is ciclopirox or octopirox, as well as their physiologically acceptable salts, especially the ethanolamine salt.

5. Product according to one of the Claims 1 to 4 characterized in that the weight ratio of 1-hydroxy-2-pyridone/crotamiton is between 4/1 and 1/4, preferably in the vicinity of 1.

6. Product that contains an anti-fungal agent selected among 1-hydroxy-2-pyridones with the general formula 1 such as defined in claims 1 to 4 and crotamiton, as the combination product for simultaneous, separated or staggered use over time for treatment of skin fungal infections. /14

7. Dermatological and/or cosmetic compound characterized in that it contains the synergistic combination of 1-hydroxy-2-pyridone and some crotamiton, as defined in claims 1 to 5, and at least one pharmaceutically acceptable excipient.

8. Compound according to Claim 7 characterized in that it contains between 0.5 and 4% by weight of the synergistic compound.